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Cold ischemic injury is reduced by the mGluR5 negative allosteric modulator MPEP in rat livers from cardiac death donors.

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Background: we previously demonstrated that the blockade of mGluR5 reduces inflammation and necrosis in both cold and warm ischemia/reperfusion injury models; in fact, the administration of 2-methyl-6(phenylethynyl) pyridine (MPEP), reduced Bax/Bcl-2, TNF- α and iNOS protein levels after the normothermic reperfusion of rat and mouse livers. In this study, we evaluated whether MPEP reduces the hepatic preservation injury in rat livers from cardiac death donors (DCD).

Methods: livers from DCD rats were isolated after an *in situ*, 30-min, warm ischemia and preserved for 22 hrs at 4°C with UW solution, then washed-out with Ringer-Lactate. 10 mg/Kg MPEP or vehicle were administered 30-min before the portal clamping and added to the UW solution (3 μ M). LDH release during washout was quantified. Liver samples were collected for WB analysis of iNOS, eNOS, NFkB, ICAM-1, caspase-3, caspase-9 and BAX.

Results: comparable levels of LDH release were detected during washout when comparing vehicle-treated DCD and MPEP-treated DCD. An increase in eNOS content occurred after MPEP treatment; iNOS expression was unchanged. NFkB and ICAM-1 expression were reduced in the MPEP-treated liver. MPEP treatment was associated with a reduced activation of the apoptosis markers caspase-3, caspase-9 and BAX.

Conclusion: these results suggest that MPEP can be used to recover cold-stored DCD livers for transplantation. In fact, MPEP donor pretreatment and organ treatment during cold storage protects against apoptosis and significantly increases eNOS, whose overexpression has been previously demonstrated to be protective in hepatic ischemia/reperfusion. Moreover, NFkB, one of the nuclear factors involved in injury progression, and ICAM-1, an NFkB target protein, are reduced after MPEP treatment. Since the current work investigated the effect of mGluR5 blockade after cold preservation only, future studies need to evaluate MPEP-induced protection after warm reperfusion as well as in rat orthotopic liver transplantation models.